REMARKS

In the Office Action dated June 28, 2006, the Examiner rejected claims 1-8, 14-20, and 22-29 under 35 U.S.C. § 101, rejected claims 1-8, 14-20, and 22-29 under 35 U.S.C. § 112, first paragraph, and rejected claims 9-21 and 29 under 35 U.S.C. § 103(a) as unpatentable over Capecchi (U.S. Patent No. 5,464,764) in view of Seth et al. (2000, Biochemical and Biophysical Research Communications 241: 535-540). In response to these rejections, Applicant has amended some of the claims, added new claim 30, but no new matter has been added.

35 U.S.C. § 101

Claims 1-8, 14-20, and 22-29 have been rejected under § 101 for lack of specific or substantial asserted utility or a well established utility. Applicant respectfully traverses. Prior to obtaining a knock out mouse, it is unforeseeable what phenotype the mouse will exhibit, and if such phenotype will correlate with a sigma-1 receptor's anticipated role in the art. It is well known in the art that not all genetic deficiencies are viable. Many knock-out projects have ended because the knock-out embryo died due to its induced genetic deficiency. Moreover, gene inactivation is not always possible because it leads the mutant animal to death during the pre-implantation period, embryonic period, or fetal period or even in the perinatal phase or immediately after birth. This fact usually leads to unknown functions of the gene product.

The counter-argument is also true. There are many cases wherein the inactivation of genes thought to be irreplaceable or essential based on previous knowledge have led to viable animals. This revelation involves the revision and correction of previous knowledge because of the demonstrated inessentiality of the gene.

Despite this uncertainty regarding knock-out mouse technology, the present invention actually discloses a viable knock-out mouse with phenotypic differences between sigma-1 receptor deficient mice and wild type mice. For instance, a significant difference in the hyper-activity response induced by (+)-SKF10047 is an overt difference with respect to wild type mice. Besides affinity for (+)-SKF10047, the present invention also discloses the phenotypic differences between wild type and sigma-1 receptor knock-out mice with regards to the effect of (+)-pentazocine as shown in Figure 14. This figure clearly demonstrates that heterozygous mice have much less sigma-1 receptor activity (function) than wild type mice and that homozygous mice have no sigma-1 receptor activity at all.

As further evidence of the phenotypic differences between wild type and sigma-1 receptor knock-out mice, Applicant respectfully submits patent application WO2006/010587, and the Affidavit of José Manuel Baeyens Cabrera in support thereof, which describes the effect of Von frey's model of allodynia

in wild type mice when compared to heterozygous or homozygous sigma-1 receptor knock-out mice obtained according to the claimed invention (see page 24, line 6). Allodynia is defined as a pain due to a stimulus that does not normally provoke pain (see page 16, line 21-22). These phenotypic differences are shown in Example 4 (page 24) and Figure 4 of WO2006/010587. In these examples, it is clearly demonstrated that sigma-1 receptor knock-out mice do not suffer from allodynia induced by capsaicin at different doses. It also demonstrates the role of sigma-1 receptors in mechanical allodynia.

Therefore, Applicants have elucidated a specific function and specific phenotype associated with such function of the sigma-1 receptor. This specific function and specific phenotype can be used for a specific and substantial purpose: to study allodynia, and drugs or treatments for such disease.

Moreover, the specification provides guidance about the role of sigma-1 receptors in processes of analgesia, addiction, depression, psychosis and schizophrenia through the following reference disclosed in the specification: Jacqueline N. Crawley, *What's Wrong with my mouse? Behavioral phenotyping of transgenic and knock-out mice*, Wiley-Liss, New York (2000). By combining this reference with the disclosed results of WO2006/010587, and the Affidavit of José Manuel Baeyens Cabrera, a well-established utility for the disclosed invention is provided.

For all these reasons, Applicant respectfully requests that the rejection be withdrawn.

35 U.S.C. § 112

Claims 1-29 have been rejected under § 112, first paragraph, for failing to comply with the written description requirement. The Examiner argues that the scope of the claims encompasses any and/or all non-human mutant mammals that are deficient in any and/or all endogenous sigma receptors, any vector that could be used for homologous recombination for making said nonhuman-mutant mammals, and any cell derived from said mammals. The Examiner then rejects claims 1-29 because the specification, while being enabling for a mouse with a sigma-1 receptor gene disruption carried out using a conventional method of gene targeting with a conventional gene targeting construct for mouse sigma-1 receptor gene, does not provide an enabled description of targeting of any other sigma receptor genes and in any other mammals besides mouse or their use. In response, Applicant has amended claims 1-3, 5-6, 8-9, 14-15, 17-18, 20-23, 25-29, cancelled claims 4, 7, 10, and 24, and added new claim 30.

Therefore, Applicant respectfully requests that the rejection be withdrawn.

Claims 1-8 and 14-29 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner sets out all the factors to be considered in regards to assessing the need for undue experimentation, and concludes that the specification does not enable one skilled in the art to make or use the invention for its fully claimed scope without undue

experimentation. In response, Applicant has amended claims 1-3, 5-6, 8-9, 14-15, 17-18, 20-23, 25-29, cancelled claims 4, 7, 10, and 24, and added new claim 30.

Further, Applicant incorporates its remarks made in response to the Examiner's § 101 rejection, and asserts that because allodynia is a specific and significant phenotype which the Applicant shows can be studied by using the claimed mutant mouse, unpredictability in the art with regards to the "hitchhiking donor gene confound" concept does not apply, as it might with less significant phenotypes.

Therefore, Applicant respectfully requests that the rejection be withdrawn.

35 U.S.C. § 103

Claims 9-21 and 29 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Capecchi (U.S. Patent No. 5,464,764) in view of Seth et al. (2000, Biochemical and Biophysical Research Communications 241: 535-540). Applicant respectfully traverses for the following reasons.

First, although the Sigma-1 receptor gene is well known, and that "knock-out" technology is an established technology, when a "knock-out" project begins, there are no reasonable expectations of success. To wit, Seth et al. discloses the basic sequence of the sigma-1 receptor gene. This sequence contains exactly 6973 nucleotides available in the GenBank #AF030199 file. Among the 6973 nucleotides, 3268 nucleotides correspond to nucleotides from the non-transcripted 5' regulatory region of the gene and 884 nucleotides correspond to the non-transcripted 3' regulatory region of the gene. However, this disclosed sequence does not arrive at the claimed construction of the homologous recombination vector and the inactivation of the gene in the claimed ES cells of the present invention.

To explain, it is well-known that the efficiency in a homologous recombination is proportional to the homology fragment, i.e., to the length of the DNA fragment that is included for recombination. Homologous recombination is inefficient with homology fragments smaller than 1000 nucleotides. Thus, the inventors first had to efficiently inactivate the Sigma-1 receptor gene by obtaining DNA clones which contained the entire gene sequence but were larger than the "known" gene sequence (less than 7 kB) disclosed in Seth et al.

To do so, the inventors obtained four bacteriophages, λSg1, λSg2, λSg5 and λSg6 (see Paragraph 84 of the specification). These bacteriophages are clones of a DNA genomic gene library and are comprised of 30,000 nucleotides, 23,000 greater that those disclosed in Seth et al. The inventors then used these clones (not the sequence disclosed in Seth et al. which was clearly insufficient for the reasons described above) to construct the disclosed homologous recombination vector, with 6800 nucleotides of homology in the 5' region and 3100 nucleotides of homology in the 3' region, both much longer than that described by Seth et al.

By means of this vector, the inventors obtained twelve recombinant clones of ES cells from 272 analyzed clones, constituting 4.4 % efficiency. As shown, Applicants respectfully assert that much of the success in obtaining a mutant mouse actually lies in the preparation of an optimal and functional homologous recombination vector that contains the maximum number of homology sequences in order to increase the recombination efficiency. Since neither Capecchi nor Seth et al. discloses nor suggests the preparation of the homology vector claimed in the present invention, including its 4.4 % efficiency, Applicant respectfully requests that the objection be withdrawn.

In addition, the recombination frequency of a certain locus of the mouse genome is unforeseeable. Not all genes can be inactivated equally, and no one can predict the homologous recombination frequency, which may vary from very high values (10-30%) to 0%. The recombination frequency lies in many factors such as the locus' sequence complexity, the presence or absence of repetitive sequences, the chromatin status, and the vector design itself. Such factors are not prima facie obvious with regards to Capecchi in light of Seth et al. Moreover, such factors create obstacles to the creation of the mutant mammal, and may ultimately lead to not obtaining it. In spite of all these obstacles, the disclosed invention claims a fertile, viable "knock-out" mouse which can give rise to viable offspring that carry the disruption in the sigma-1 receptor. This implies that the mutation has been stabilized in the knock-out animal's genome. These results provide proof of the success of the vector design disclosed and claimed in the present invention for homologous recombination, a success not obviated by Capecchi in light of Seth et al.

Finally, one of the most important factors affecting the feasibility of a "knock-out" project is the ability of the scientific team. While one scientific team might be able to obtain a "knock-out" mouse defective in a certain gene, another scientific team working in parallel may not be able to obtain such mouse. This ability results from the capacity of the scientific team to obtain a functional and optimal recombination vector. Indeed, up to now, no other scientific team besides the inventors of the claimed invention have disclosed a "knock-out" mouse defective for the sigma-1 receptor. This is so despite the fact that Capecchi teaches the "knock-out" technology and Seth et al. discloses the sigma-1 receptor gene sequence. As an important example, not even Ganapathy's group which described the sigma-1 receptor gene sequence in Seth et al. has been capable of obtaining the claimed invention.

Therefore, for all these reasons, the claimed invention is not unpatentable over Capecchi (U.S. Patent No. 5,464,764) in view of Seth et al. (2000, Biochemical and Biophysical Research Communications 241: 535-540). Thus, Applicant respectfully requests that the rejection under § 103(a) be withdrawn.

Conclusion

In view of the remarks set forth below, Applicants respectfully submit that the present invention is in condition for allowance.

Respectfully submitted,

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